

two or more times a day. As explained in the specification, such administration is quite inconvenient, especially for children and adolescents who must take a dose at school, and can lead to abuse. Applicants have discovered that this is **not** a circumstance which is appropriately dealt with by providing the drug in sustained or extended release form, in that it is believed that the onloading and offloading of the drug is related to its therapeutic profile. Rather, Applicants have discovered that it is desirable to effect a pulsatile pattern of administration, as is experienced when the drug is taken at two times during the day.

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The claimed dosage forms and methods of administration permit the once daily administration of drug, but give rise to plasma levels of drug in patients which reflect pulsatile administration. That is, the present dosage forms effect two or more effectively separate administrations of the drug separated by a predetermined time period -- a pulsatile dosage form. It is believed that there is no disclosure in the prior art of these advantages of using such a dosage form for treatment with a phenidate drug.

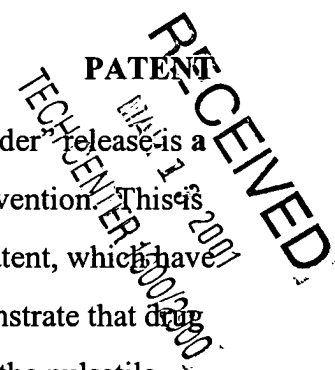
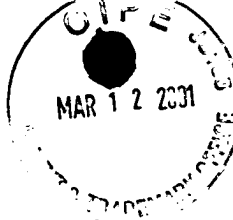
The protest cites three references: U.S. Patent No. 5,133,974 to Paradissis et al. (hereinafter "the 974 patent"), Canadian Patent No. 1,297,368 to Alza Corporation (hereinafter "the 368 patent") and U.S. Patent No. 5,580,578 to Oshlack et al. (hereinafter "the 578 patent"). Each of these references will be discussed in turn.

The 974 Patent

The protest alleges that the 974 patent describes extended release multiparticulate dosage forms that have the delayed release dosage characteristics described by the present claims. However, contrary to the assertions of the protest, the 974 patent **does not describe a pulsatile dosage form**. Rather, the 974 patent is directed to extended release dosage forms that are adapted to produce **zero order** release of drug over a 12 to 24 hour time period. See the 974 patent at column 3, lines. 20-21 and lines 57-58; and at col. 9, lines 27-30. The 974 patent also describes its dosing profile as being formulated to permit a release of drug from its particles "over a 12 to at least 24 hour period" (see, for example column 6, lines 27-33) and wherein

... less than 50% of the drug is released within 1 hour of measurement and not less than 70% of the drug is released at the targeted dosing period, such as a 12 to at least 24 hour period.

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974 Patent at column 6, lines 37-40. It will be readily appreciated that a "zero order" release is a **constant** rate of release, and certainly **not pulsatile** as required by the present invention. This is further made clear by the dissolution results shown in the examples of the 974 patent, which have been reproduced in graphic form in Exhibit 2, attached hereto. These data demonstrate that drug is released from the 974 compositions continuously over time,² and do not show the pulsatile release described by the present claims.

The protest states on pages 3-4 that the phrase "delayed release" provided in the present specification "includes" the controlled release parameters described in the 974 patent, which are said to be "...less than 50% of the drug released within 1 hour of measurement and not less than 70% of the drug released at the targeted dosing period." This, however, is simply not correct. The definition of "delayed release" provided in the present specification states that the profile "includes a period during which no more than about 10 percent of the drug in a particular dosage form is released..."; thus, giving rise to a pulsatile release. This feature is not taught or suggested anywhere in the 974 patent, or in the examples thereof.

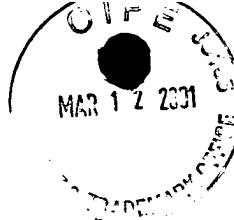
The 974 patent neither discloses nor suggests the invention of the present claims.

The 368 Patent

The protest asserts that the Canadian claims are obvious in view of the 368 patent, which is said to disclose dosage forms that provide delivery of a drug in a pulsed manner. The protest expends much effort describing why, in its opinion, it would have been obvious to use the ammoniomethacrylate copolymers recited in the Canadian claims (and in present claims 1 and 4-8) in the dosage form described in the 386 patent, and then to use a sufficient amount thereof to achieve a pulsatile release. Significantly, however -- **and as the protest admits** -- the 368 patent **does not disclose or suggest a pulsatile release for a methylphenidate drug**. There is simply no teaching whatsoever in the 368 patent of the particular benefits of pulsatile administration as applied to a phenidate drug that have been discovered by Applicants. Thus, regardless of what copolymers are used in the of 386 formulation, the 386 patent cannot be said to render the present claims obvious.

² According to the U.S. Pharmacopeia, the test method employed in the 974 patent is an in vitro method in which release of drug from the dosage form into surrounded medium is measure over time.

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There are other reasons why this argument is without merit. The protest argues at page 6 that because amminomethacrylate copolymers were known to be used in sustained release formulations, it would have been obvious to

...increase the amount of ammonio methacrylate copolymer sustained release coating conventionally used to an amount above the maximum amount for sustained release so that delayed release is achieved.

However, there is no teaching anywhere in the art to support this view. It amounts to rank speculation. Indeed, the protest itself admits that ammoniomethacrylate copolymers would have to be used in an amount that is "above the maximum amount for sustained release" to achieve a pulsatile release dosage form, which is certainly at an amount that would defeat the purpose for its inclusion in a **sustained release** formulation of the prior art patent. Thus, the 386 patent, if anything, teaches away from the present invention. Clearly, the presently claimed dosage forms are not obvious in view of such a disclosure.

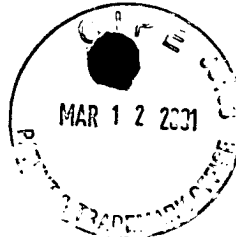
The 578 Patent

The protest asserts that the formulations of the Canadian claims are obvious in view of the 578 patent, which is directed to solid controlled release formulations that are stable to exposure to accelerated storage conditions. The protest appears to base its assertion of obviousness on the 578 patent's alleged disclosure of certain fillers, curing times and coatings similar to some utilized in the examples of the present specification. However, the 578 patent neither discloses nor suggests pulsatile release as described by the present claims or the use of such a regime with a phenidate drug. Accordingly, the present claims cannot be obvious from this reference.

The protest also argues that Canadian claim 23 is anticipated by the 578 patent. While no counterpart to this claim is currently pending in the present application,³ Applicants nevertheless note that the 578 patent neither discloses nor suggests any use of a phenidate drug, which is an explicit element of the claim.

³ A corresponding claim has issued in the patent resulting from the parent application, U.S. 5,837, 284.

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TECH CENTER 1600/2900**The Combination of the 974 and 578 Patents**

The Protest also asserts that the claims obvious in view of the combination of the 974 and 578 references, on the basis that the 578 patent teaches controlled release particles, and the 974 patent teaches combining controlled release particles with immediate release particles. However, neither reference discloses or suggests a pulsatile release for a methylphenidate drug. As there is no teaching whatsoever in the cited art of the pulsatile administration of a methylphenidate drug, the art cannot be said to render the present claims obvious.

Other Newly Cited Art

In addition to the art cited in the protest, Applicants also have cited in their Information Disclosure Statement and accompanying form PTO-1449 the following references that have recently come to their attention, copies of which are provided herein.

PCT/FI92/00242 (WO 93/05769) discloses long-acting oral compositions from which the release of active component increases exponentially with time. The compositions are said on page 2, lines 30-32 to "not release the active compound discontinuously in bursts but primarily following an exponential release pattern."

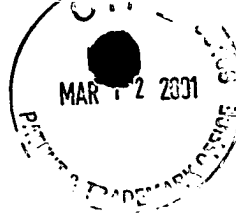
Each of PCT/US97/13816 (WO 98/06380) and PCT/US97/22016 (WO 98/23263) discloses dosage forms that provide sustained and ascending drug release patterns.

PCT/US97/16599 (WO 98/14168) discloses dosage forms that provide sustained and ascending drug release patterns. Example 6 of the PCT/US97/16599 describes several such delivery systems for methylphenidate, including those depicted in Figures 12, which is said to illustrate

... 30 mg delivered three times delivered three times a day by the solid line, an ascend dose from a dosage form comprising 36 mg of drug once a day by the dash line, and a dosage form comprising an immediate 8 mg dose and a sustained 26 mg ascending dose illustrated by the dot-dash line.

PCT/US97/16599 at page 22, lines 1-4. Figures 13-16 are said to show similar profiles, with different ascending and immediate release dosages. While the dosage of the "dot-dash" lines of Figures 12-16 appear to have two "pulses" of drug delivery, there is nothing in the PCT/US97/16599 application to indicate that the "ascending" and "immediate release" dosages are contained within a single dosage form, or that such a dosage form was prepared.

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U.S. 4,968,505 to Okada et al. discloses a sustained release dosage form of diclofenac sodium.⁴

U.S. 5,308,348 to Balaban et al. ("the 348 patent") discloses a mechanical delivery device that is said to provide a pulsatile effect. The 348 patent states that its disclosed dosage form can be used to achieve a wide variety of intervals between pulses:

... which may be from minutes to days and may be as short as two or three minutes, although it is typically from about six hours to about 120 days and preferably within the range of from about six hours to about twenty days.

348 patent at column 4, lines 56-60. The 348 patent provides at column 11, line 57 to column 12, line 46 an extensive list of over 150 drugs that are said to be capable of being delivered by its disclosed devices, including methylphenidate hydrochloride. However, the 348 patent does not specifically describe any particular embodiment using a phenidate drug, or such an embodiment having the delayed release profile of the presently claimed dosage forms.

U.S. 5,223,265 to Wong ("the 265 patent") discloses a fluid-imbibing drug delivery device for the initially delayed delivery of an active agent, followed by continuous delivery of the agent over a prolonged period of time. The 265 patent provides at column 7, line 50 to column 8, line 27, an extensive list of over 50 general types of compounds that are said to be capable of being delivered by its disclosed devices, and a further list at column 8, line 28 to column 9, line 15, of over 140 specific agents that are said to be capable of being delivered by its disclosed devices, including methylphenidate hydrochloride. However, the 265 patent does not describe any specific embodiment including a phenidate drug, and the release profile of the presently claimed dosage forms.

U.S. 5,156,850 to Wong ("the 850 patent") and its division U.S. 5,232,705 to Wong ("the 705 patent"), each disclose a dosage form that is said to provide rate programmed drug delivery at time-varying patterns. The dosage form is said to be capable of providing a number of different dosing profiles, including providing an instant-pulse dose of a therapeutic drug, followed by a delayed delivery of drug, and then delivering a dose of drug. The patents provide a list (at column 9, line 57 to column 11, line 47 of the 850 patent) of over 60 general types of

⁴ The 505 patent is believed to be the U.S. counterpart to reference AM cited on Applicants' form PTO-1449.

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drugs, and a further list of over 140 specific agents that are said to be capable of being delivered by its disclosed devices, including methylphenidate hydrochloride. However, the reference does not specifically describe any embodiment including a phenidate drug and having the delayed release profile of the presently claimed dosage forms.

U.S. 5,874,090 to Baker ("the 090 patent") discloses sustained release formulations of d-threo-methylphenidate. The 090 patent does not disclose the release profile of the presently claimed dosage forms.

PCT/US99/11920 (WO 99/62496) discloses oral dosage form that are said to release a drug at an ascending rate of release over an extended period of time.

The claims presently before the Examiner patentably define the invention over the art and are otherwise in condition for allowance. An early Office Action to that effect is, therefore, earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Respectfully submitted,


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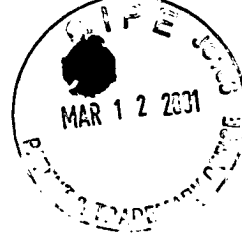
Date: March 7, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 2, 9 and 10 have been canceled without prejudice.

New claims 13 and 14 have been added.

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